a1

f. admixing a second assay reagent with the test sample in said second receptacle to form a homogenous suspension prior to conducting a first assay;

g. incubating said samples under predetermined conditions;

h. analyzing said suspensions independently and individually by at least two different assays, wherein one of said first and said second assays is a turbidimetric assay and the other is a fluorescent assay; and

i. simultaneously determining a microorganism's identify and susceptibility to an antimicrobial agent.

a2

26. The method of claim 22 wherein said incubating step g and said analyzing step h includes the application of the algorithm outlined in Figure 1.

Election/Restriction

The Applicants respectfully affirm the election of claims 22-36 is the present application. Therefore, the Applicants cancel claims 1-~~21~~ and 37-~~42~~ without prejudice to filing these claims in continuation and/or divisional applications.

Claim Rejections under 35 USC § 112 Second Paragraph

The Examiner has rejected claims 22 and 26 under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as their invention. Specifically, the Examiner has rejected claim 22 as being incomplete for omitting essential steps. Claim 22 has been amended to include new step "i" which recites the final process of "simultaneously determining a microorganism's identify and susceptibility to an antimicrobial agent."

Furthermore, the Examiner states that claim 22 is unclear because it implies the process is for identifying the antimicrobial agent not the microorganism. The preamble of claim 22 has been amended to clarify the Applicants' intentions.

Finally, the Examiner has rejected claim 26 because the algorithm of Figure 1 recited in claim 26 could require further incubation, a process not included in step "h" of claim 22. The Applicants have amend claim 26 to include the incubating step of claim 22, step "g."

Based on the amendments to claims 22 and 26, the Applicants respectfully assert that the Examiner's rejections under 35 USC § 112, second paragraph have been traversed and request their withdrawal.

Claim Rejections Under 35 USC § 102(b)

The Examiner has rejected claims 22-28 and 32-36 under 35 USC § 102(b) as being anticipated by United States patent number 5,164,301 to Thompson et al. (herein after "the Thompson reference"). Before addressing the specifics of the Examiner's 35 USC § 102(b) rejection, the Applicants believe that a brief review of the invention will significantly advance the prosecution process.

Briefly, the present invention is an automated system for the rapid simultaneous identification of a microorganism and the determination of its susceptibility to antimicrobial agents. Basically, one representative embodiment of the present invention is a "hybrid panel" consisting of a multi-well solid support inoculated with a homogenous mixture of microorganism (the "sample"). Two sets of wells are inoculated per sample. One set of wells contains a nutrient broth having different antimicrobial agents at various concentrations (the Minimum Inhibitory Concentration (MIC) wells). A second set of wells contains nutrient broth and different metabolizable substrates (the microbial identification (ID) wells). Growth of the microorganism and/or utilization of the metabolizable substrates is determined by one of two methods. In one embodiment of the present invention, the MIC is determined using a rapid turbidimetric method and the microbial ID is determined via fluorescent methods. This process is facilitated by the use of a modified clear plastic plate that prevents fluorescent cross-talk between wells. Moreover, the methods and systems of the present invention are enhanced by the use of a variety of hardware and software systems resulting in a smart, automated, hands-free system having the registered trademark WalkAway®.

Prior to the present invention, conventional and semi-automated MIC and/or ID systems relied on either chemical or turbidimetric methods for assessing substrate utilization and/or microbial growth. Both of these methods have relative advantages and disadvantages. Turbidimetric methods are extremely specific and considered the gold standard for MIC testing because they conclusively demonstrate the static or cidal effects of an antimicrobial agent. If an organism can thrive in the antimicrobial's

presence, then the microorganism will reach a critical mass (population) that is detectable using spectrophotometric or visual methods. However, prior to the present invention, it was believed that this required a minimum of 18 to 24 hours before definitive results could be obtained.

On the other hand, microbial ID systems commonly relied on the presence of trace amounts of enzymes to react with substrates present in the ID wells. The reaction of the enzymes with the substrates could be detected using exquisitely sensitive chemical methods that did not depend on microbial growth. Consequently, rapid, accurate microbial ID systems using fluorescent detector systems, among others, have been quickly developed and deployed. However, MIC values continued to be delayed for up to 24 to 48 hours after the microbial ID was available. Consequently, prior to the present invention, it was thought that chemical methods such as the fluorescent techniques used for microbial ID were the only way to decrease MIC turn-around-time (the time from sample receipt to result report). As a result Thompson and others developed MIC systems that depended on chemical indicators of growth such as fluorescence.

While chemical growth detection MIC methods are presently in use, they are prone to sacrificing accuracy in sake of speed. Therefore, in order to provide medical practitioners the benefit of rapid MIC turn-around-times without the need for sacrificing accuracy, the present inventors sought to develop a combined MIC/ID system that utilized the gold standard for MIC determination (turbidimetric) with an optimized rapid ID system (fluorescent technology).

This daunting challenge was made possible by the present inventor's surprising discovery that contrary to commonly held principles of microbial population detection dynamics, turbidimetric methods were in fact as sensitive as fluorescent and other indirect measurements of microbial growth, but possessed specificity not presently achievable by chemical methods (see the present specification at page 17 beginning at line 2). Therefore, based on this surprising discovery, the present inventors were able to develop an optimized, hybrid MIC/ID system that utilized the preferred method of detecting microbial substrate utilization (ID) with the gold standard for MIC determination (turbidimetric). Unlike the prior art, the present invention utilizes a multi-

well (microtiter plate in one embodiment) support with clear plastic wells that permits rapid and sensitive fluorescence and turbidimetric determinations simultaneously in the minimum period of time.

The Examiner asserts that the Thompson reference anticipates the present invention because it discloses the simultaneous measurement of turbidity and fluorescence on a parallel sample. The Examiner cites column 12 lines 2-5 of the Thompson reference. The Applicants respectfully assert that the Examiner has misinterpreted, or in the alternative misapplied, the cited passage in the Thompson reference.

It is axiomatic in Patent Law that "[a]nticipation is established only when a single prior art reference discloses expressly or under the principles of inherency, each and every element of the claimed invention." *RCA Corp. v. Applied Digital Data Systems, Inc.*, (1984, CA FC) 221 U.S.P.Q. 385. The standard for lack of novelty, that is, for "anticipation," is one of strict identity. To anticipate a claim, a patent or a single prior art reference must contain all of the essential elements of the particular claims. *Schroeder v. Owens-Corning Fiberglass Corp.*, 514 F.2d 901, 185 U.S.P.Q. 723 (9th Cir. 1975); and *Cool-Fin Elecs. Corp. v. International Elec. Research Corp.*, 491 F.2d 660, 180 U.S.P.Q. 481 (9th Cir. 1974). In the present Office Action, the Examiner's rejection is based on the Thompson reference, which fails to show all of the essential elements of the instant invention.

Column 12, lines 2-5 of the Thompson reference discloses a controlled experiment in which those inventors sought to demonstrate by comparative analysis that the Thompson rapid fluorescent MIC procedure was as sensitive and specific as the gold standard turbidimetric method that had been incubated for 18 hours. Nowhere in the cited passage, or anywhere else in the Thompson reference is a combined, hybrid method using a rapid fluorescent microbial ID assay run in parallel with a rapid turbidimetric MIC assay disclosed. In the Thompson reference, the turbidimetric assay was used as a process validation control that compared the fluorescent MIC assay disclosed in Thompson with the previously accepted standard turbidimetric assay. The turbidimetric assay disclosed at column 12, lines 2-5 of the Thompson reference is NOT part of Thompson's analytical system, rather the assay system disclosed in the

Thompson reference is entirely fluorescent based whether used for MIC or ID determinations. This is in sharp contrast to the hybrid analytical system of the present invention.

The claims rejected under 35 USC § 102(b) of the present invention disclose and claim a hybrid analytical system wherein BOTH a turbidimetric and a fluorescent assay are used simultaneously to perform two DIFFERENT analyses. Thus, while the Thompson reference may teach similar data, the reference does not disclose a hybrid analytical system wherein BOTH a turbidimetric and a fluorescent assay are used simultaneously to perform two DIFFERENT assays.

Therefore, the present claims patentably distinguish over the Thompson reference and the Applicants respectfully assert that the Examiner's rejection under 35 USC § 102(b) has been traversed and request its withdrawal.

Claim Rejections Under 35 USC § 103(a)

The Examiner has rejected claims 22-36 under 35 USC § 103(a) as being unpatentable over the Thompson reference (United States patent number 5,164,301) in view of the Fisher Biotechnology Catalogue (hereinafter "the Fisher reference").

In order to establish a prima facie case of obviousness, the Examiner has the burden of establishing three basic criteria: 1) there must be some motivation, either in the prior art cited by the Examiner, or in the general knowledge available to one of ordinary skill in the art, to modify the reference or combine the references being relied on to reject the claimed invention; 2) the Examiner must demonstrate that there would be a reasonable expectation of success; and 3) the prior art reference or combination must teach all of the requirements of the claimed invention. The Applicants respectfully assert, for the reasons more fully developed below, that the Examiner has not met this burden and therefore, all rejections predicated on obviousness are traversed.

Case law makes clear that the best defense against hindsight-based obviousness analysis is the rigorous application of the requirement for a showing of a teaching or motivation to combine the prior art references *In re Dembiczak,* 175 F.3d at 999, 50 USPQ2d at 1617. The absence of a convincing discussion of the specific sources of the motivation to combine the prior art references is a critical omission in the

Examiner's obviousness analysis, which mainly discusses the way that the multiple prior art references can be combined to read on the claimed invention.

The Applicants respectfully assert that the Examiner has not carried this burden. The Court of Appeals for the Federal Circuit (CAFC) recently summarized the law of obviousness as it relates to hindsight and 35 U.S.C. §103(a) rejections in *In re Dembiczak* 50 USPQ 2d. 1614 (Dec. 1999). Quoting Judge Clevenger:

> "Our case law makes clear that the best defense against the subtle but powerful attraction of hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teachings or motivation to combine prior art references. See, e.g. C.R. Bard, Inc. v. M3 Sys., Inc. 157 F,3d 1340, 1352, 48 U.S.P.Q. 2D (BNA) 1225, 1232 (Fed. Cir. 1998) (describing "teaching or suggestion or motivation [to combine] as an essential evidentiary component of an obviousness holding"); In re Rouffet, 149 F.3d 1350, 1359, 47 USPQ 2d (BNA) 1453, 1459 (Fed. Cir. 1998) ("the Board must identify *specifically*...the reasons one of ordinary skill in the art would have been motivated to select the references, and combine them"); In re Fritch, 972, .2d 1260, 1264, 23 USPQ 2d (BNA) 1780, 1783, (Fed. Cir. 1992) (*examiner can satisfy burden of obviousness in light of combination "only by showing some objective teaching [leading to the combination]*"); In re Fine, 837 2d. 1071, 1075, 5 USPQ 2d (BNA) 1596, 1600 (Fed. Cir. 1990) (evidence of teaching or suggestion "essential" to avoid hindsight); Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F. 2d 281, 297, 227 USPQ (BNA) 647, 667 (Fed. Cir. 1985) (district court's conclusion of obviousness was error when it "did not elucidate any *factual teachings, suggestions or incentives from the prior art that showed the propriety of combination*")
>
> ...The *range of sources available, however, does not diminish the requirement for actual showing.* ***That is, the showing must be clear and particular. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not "evidence."*** (Emphasis added.)

The Applicants respectfully assert that the Examiner has not provided *any* objective evidence of motivation to combine the Thompson and Fisher references based on knowledge generally available to one of ordinary skill in the art at the time the invention was made. Furthermore, the Examiner in combining the Thompson and Fisher references without evidence of such suggestion, teaching, or motivation to combine same, simply takes the inventor's disclosure as a blueprint to defeat patentability. The Applicants respectfully assert that Examiner's use of the present application as a "blueprint to defeat patentability" is the very essence of hindsight that Judge Clevenger cautioned Examiner's against doing in *In re Dembiczak.*

The Thompson reference combined with the Fisher reference does not disclose all of the elements of the present invention. As previously stated, the Thompson reference does not disclose a hybrid analytical system wherein BOTH a turbidimetric and a fluorescent assay are used simultaneously to perform two DIFFERENT assays. The Thompson reference only discloses a fluorescent method of detecting microbial activity. Not a hybrid system having the capacity to accurately and SIMULTANEOUSLY determine both MIC values and microbial IDs using two different analytical techniques.

The Fisher reference does nothing to cure this deficiency. The Fisher catalogue is a non-enabling reference that merely provides a depiction and brief description of a microtiter plate for the explicit use[1] in fluorescent assays. Therefore, the Thompson reference and the Fisher reference combine to teach fluorescent methods only. It would be entirely serendipitous for a person having ordinary skill in the art to think of using the Fisher plate for turbidimetric assays based solely on the combined teachings of Thompson and Fisher. Furthermore, the surprising insight and discovery of the present inventors who demonstrated the equivalent sensitivity of turbidimetric assays with fluorescent assays for detecting microbial growth, would still be necessary to practice the present invention. Absent such insight, at best, a person having ordinary skill in the art would have combined the teaching of Fisher and Thompson to develop two independent assays both utilizing fluorescent measurements and employing the

[1] The Examiner in his April 17, 2001 Office Action reiterates the "explicit use" of the Fisher Biotechnology microtiter plate at page 6, line 2.

modified Fisher microtiter plates. Nothing in Fisher or Thompson teaches the surprising discovery taught by the present application.

Therefore, the Applicants respectfully assert that the Examiner's 35 USC § 103 (a)rejection of claims 22-36 has been traversed and request that this rejection be withdrawn.

In view of the foregoing, it is submitted that all pending claims are now in good condition for allowance. Allowance is respectfully requested.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changed made**."

If for any reason direct communication with Applicants' attorney would serve to advance prosecution of this case to finality, the Examiner is invited to call the undersigned attorney at the below listed telephone number.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 16-2230.

Respectfully submitted,

October 1, 2001

Louis C. Cullman
Registration No. 39, 645

ext. 6013

OPPENHEIMER WOLFF & DONNELLY LLP
840 Newport Center Drive, Suite 700
Newport Beach, CA 92660
Telephone: 949.823.6000
Facsimile: 949.823.6100